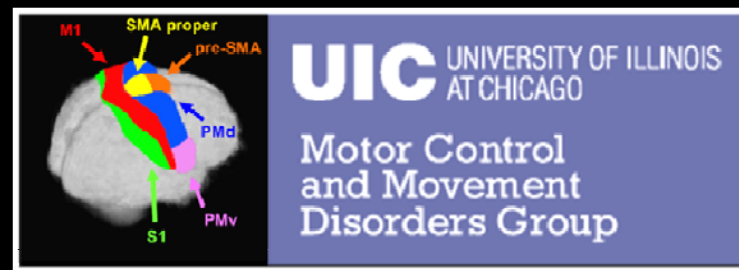# Diffusion Tensor Imaging:
## Parkinson's Disease and Atypical Parkinsonism

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Bioengineering, and Neurology



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San Francisco, CA

# Characteristics of Parkinson's disease

- **Prevalence rate PD** (Moghal et al., 1994)
  - general population = 0.3%
  - 50-70 = 1%
  - > 65 = 3%

- **Primarily a motor disorder**
  - Tremor, bradykinesia, and rigidity
  - Affects activities of daily living such as eating, cooking, grooming
  - Also affects cognition, depression, anxiety, sense of smell

- **Structural and physiological changes**
  - Loss of neurons in SNc (McGeer et al., 1977)
  - PET studies show reduced dopamine uptake in the striatum (Brooks, 1990)

# Major problems for current research

- There is no definitive diagnosis for PD, PSP, MSA, and ET while the person is alive

- It can be difficult to diagnose these diseases early

- Important to diagnose these diseases early and accurately because the prognosis is different

- Symptomatic treatments for PD, PSP, MSA, and ET are already different

- Disease modifying treatments could be different
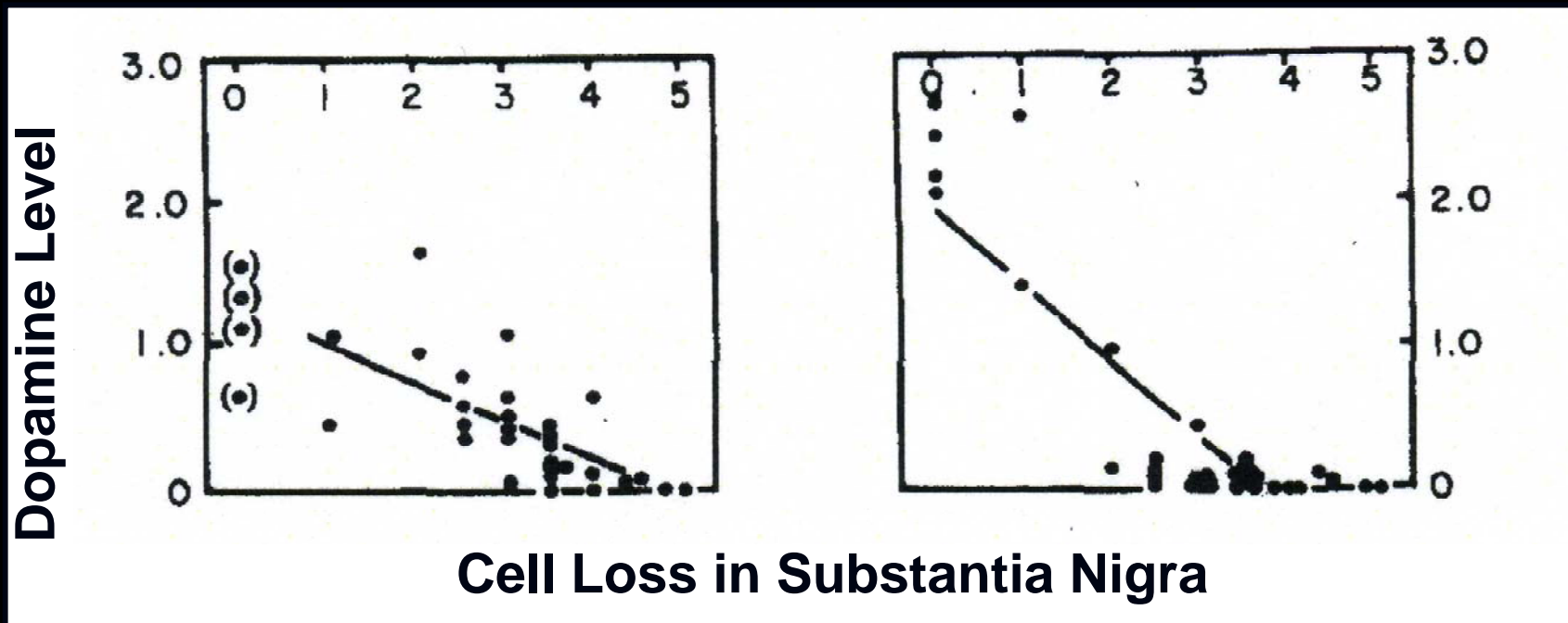
# What to focus on today

- Diffusion tensor imaging of the substantia nigra:
    - Early stage drug naïve Parkinson's disease
    - Healthy aging
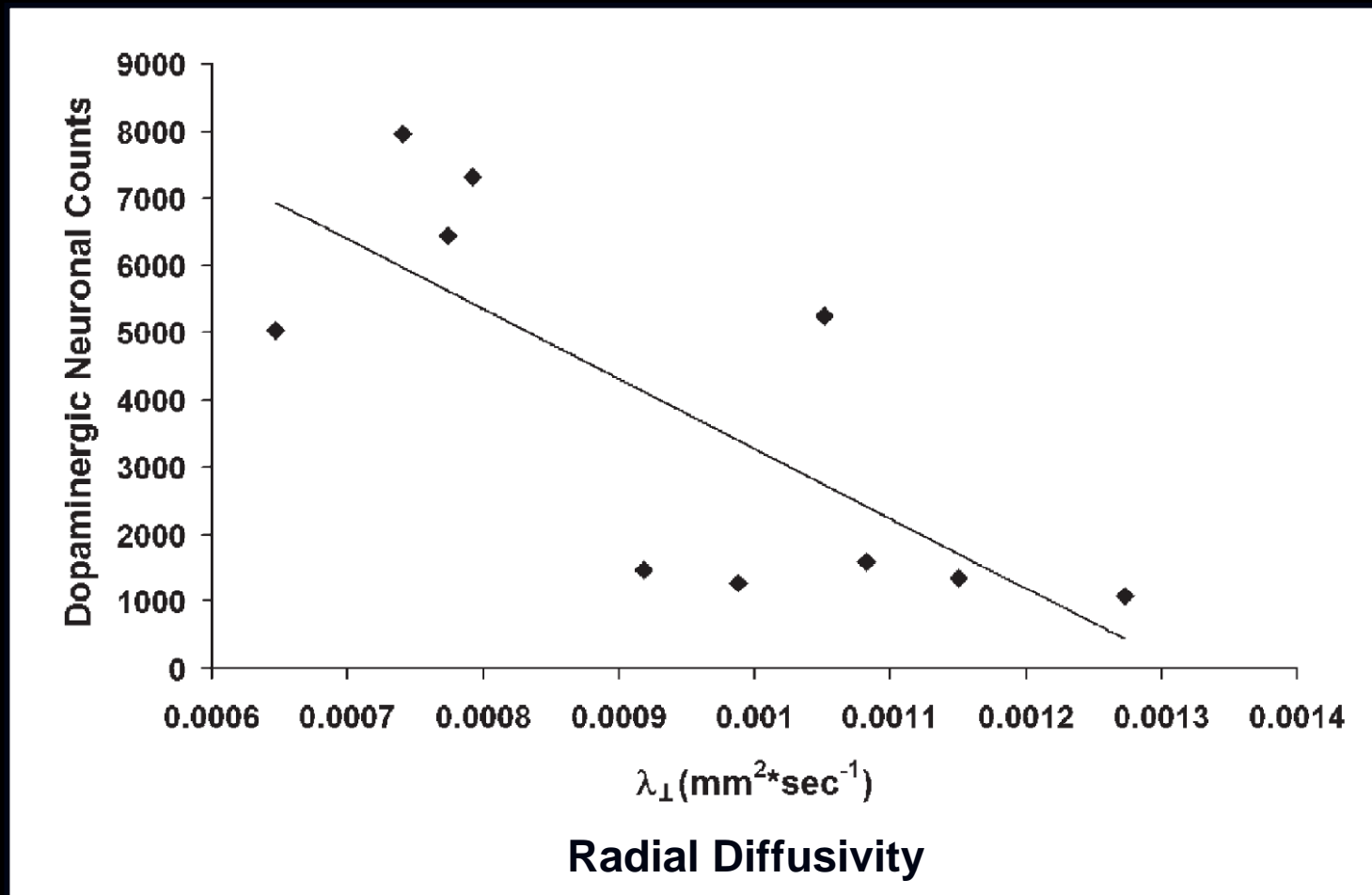    - Atypical Parkinsonism and Essential Tremor
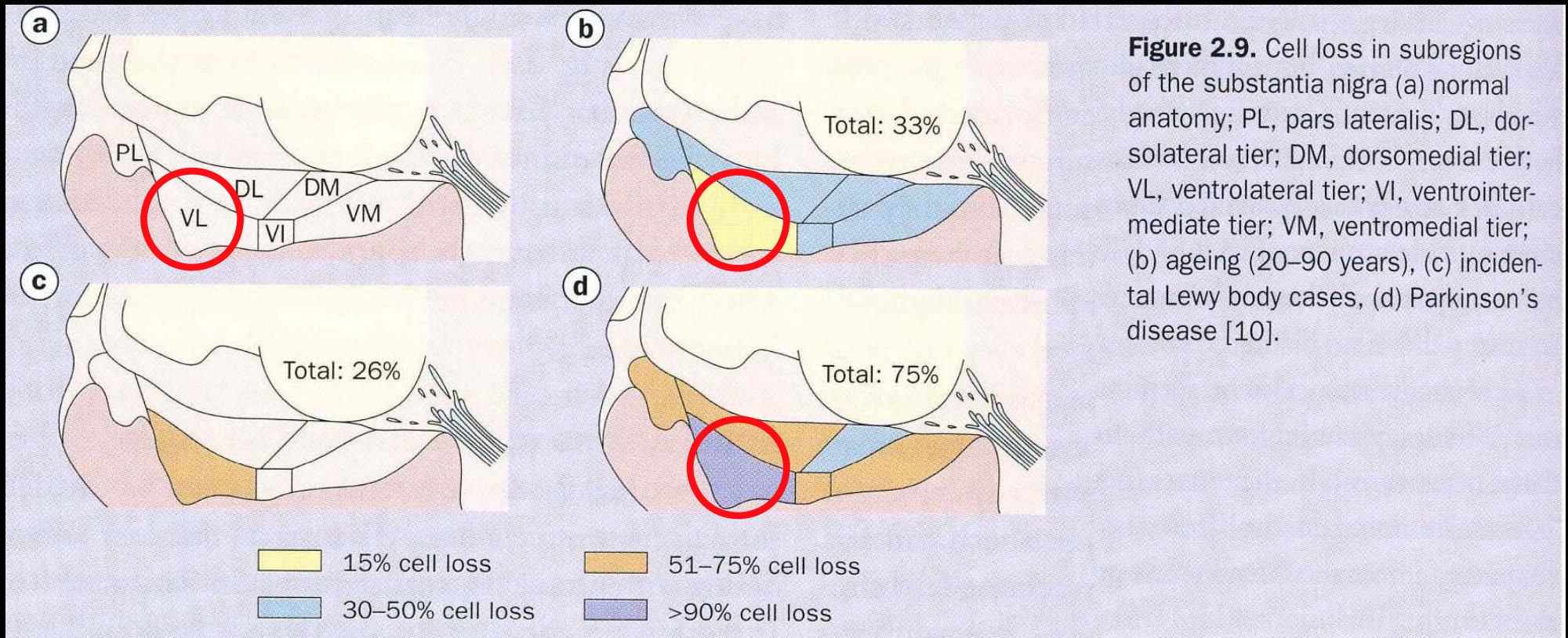
# Cell Loss in PD



Caudate Nucleus

Putamen

Cell Loss in Substantia Nigra

Bernheimer et al. J Neurol Sci. 1973.

# Dopamine cell loss correlates with DTI in mouse model of PD

# Ventrolateral tier of the substantia nigra most depleted in PD



Figure 2.9. Cell loss in subregions of the substantia nigra (a) normal anatomy; PL, pars lateralis; DL, dorsolateral tier; DM, dorsomedial tier; VL, ventrolateral tier; VI, ventrointermediate tier; VM, ventromedial tier; (b) ageing (20–90 years), (c) incidental Lewy body cases, (d) Parkinson's disease [10].

Differs from age related neuron loss which has a sparing of ventral lateral tier with aging

# Study design

- 14 early stage, de novo PD patients
  - Average age: 57 years
  - UPDRS motor range =  4 to 32
  - UPDRS mean 17
- 14 age and sex matched control subjects
- DTI sequence
  - 3T GE; 8-channel head coil; matrix = 256x256; 4mm slices; 15 slices; NEX = 4; b = 0, 1000; TR = 4500 ms; TE = 82 ms; 27 directions;
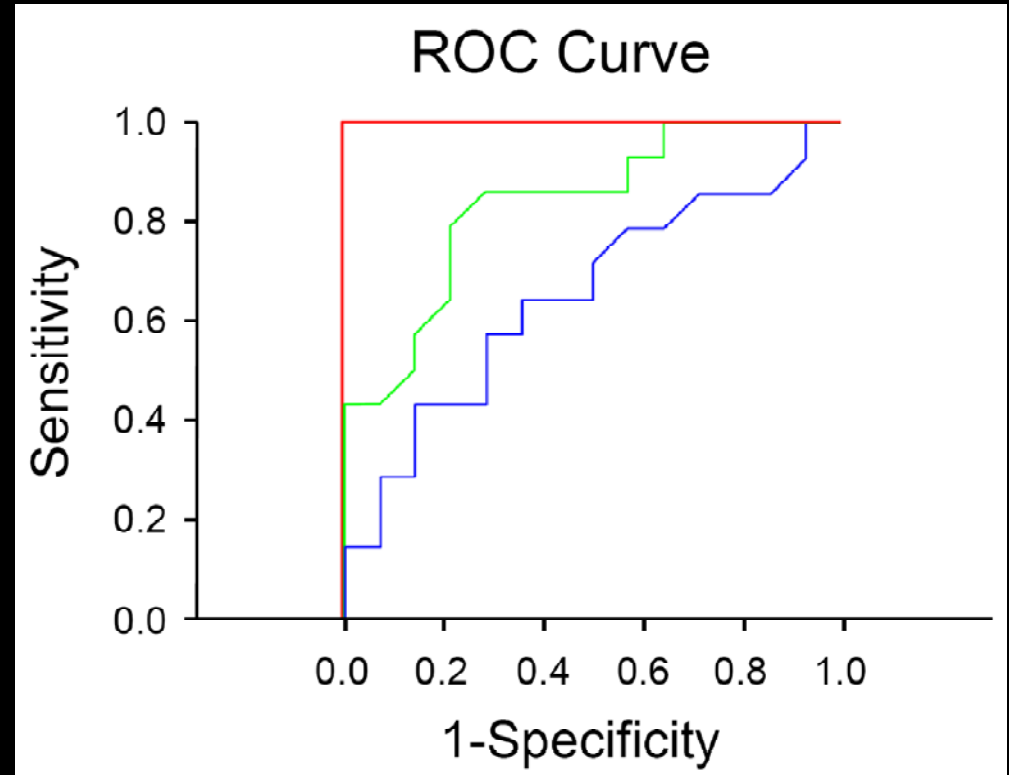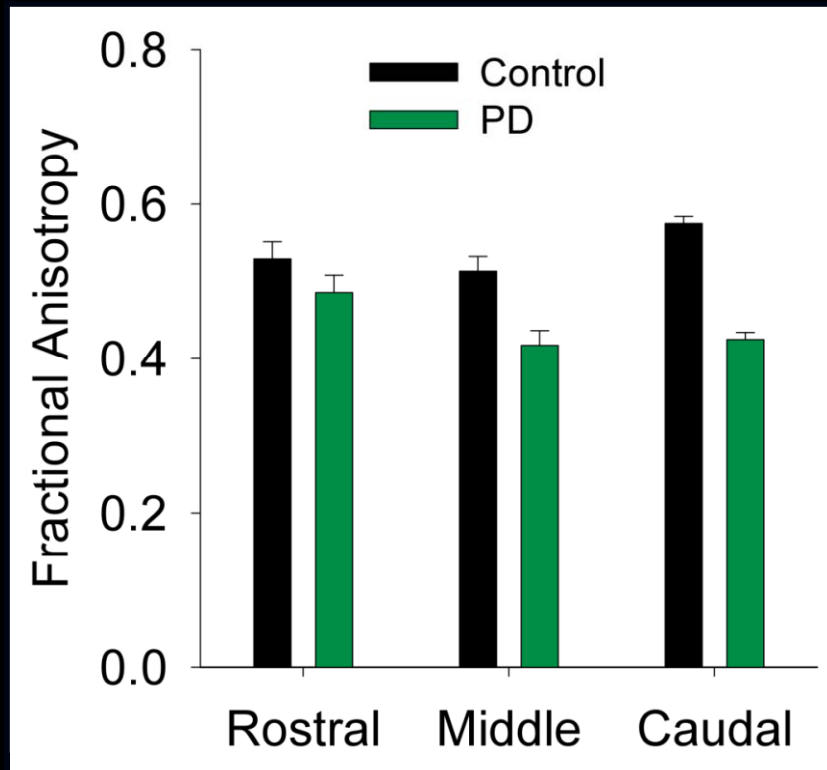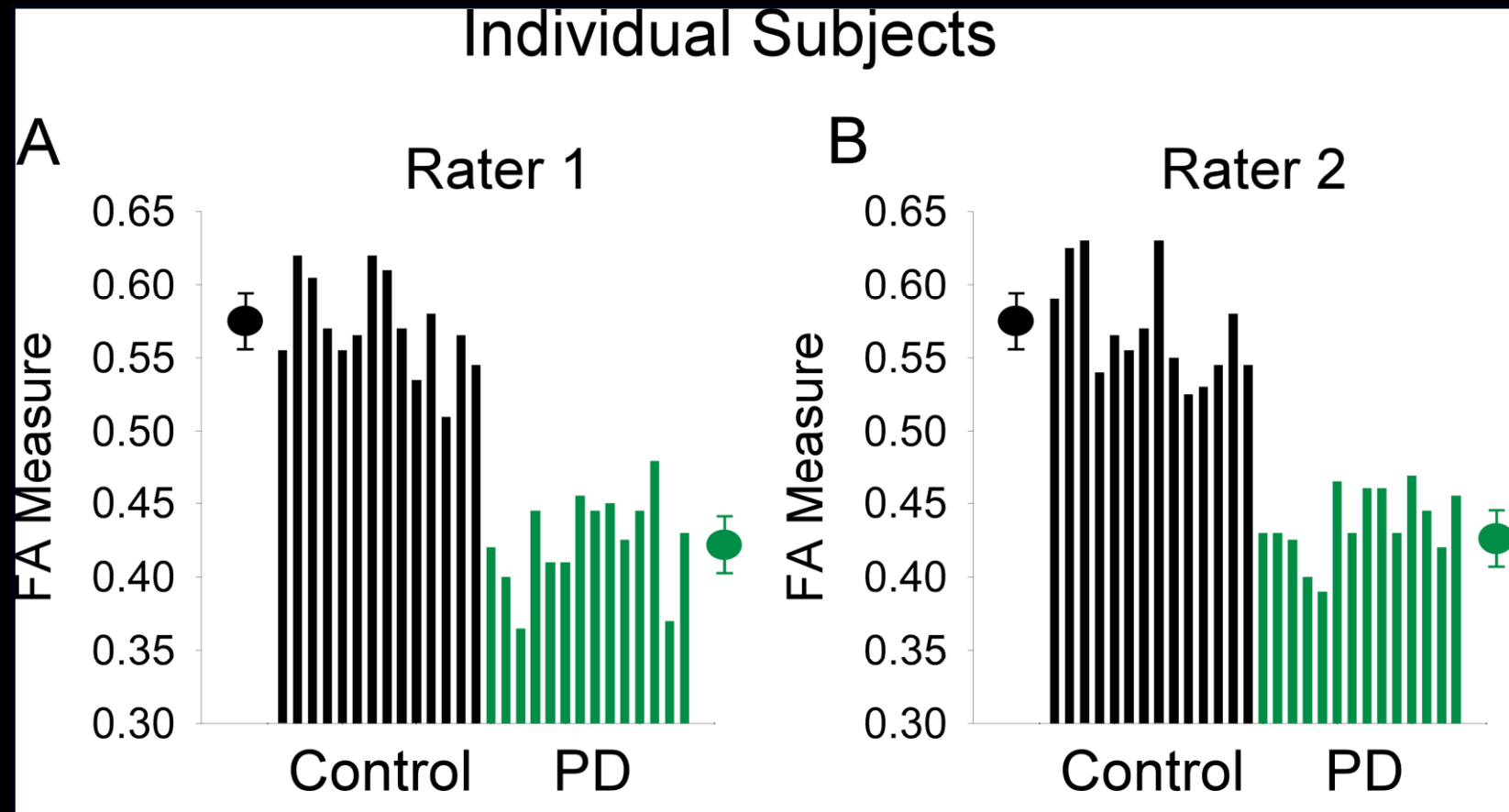
**A   Dorsal B0 Image**

Red Nucleus

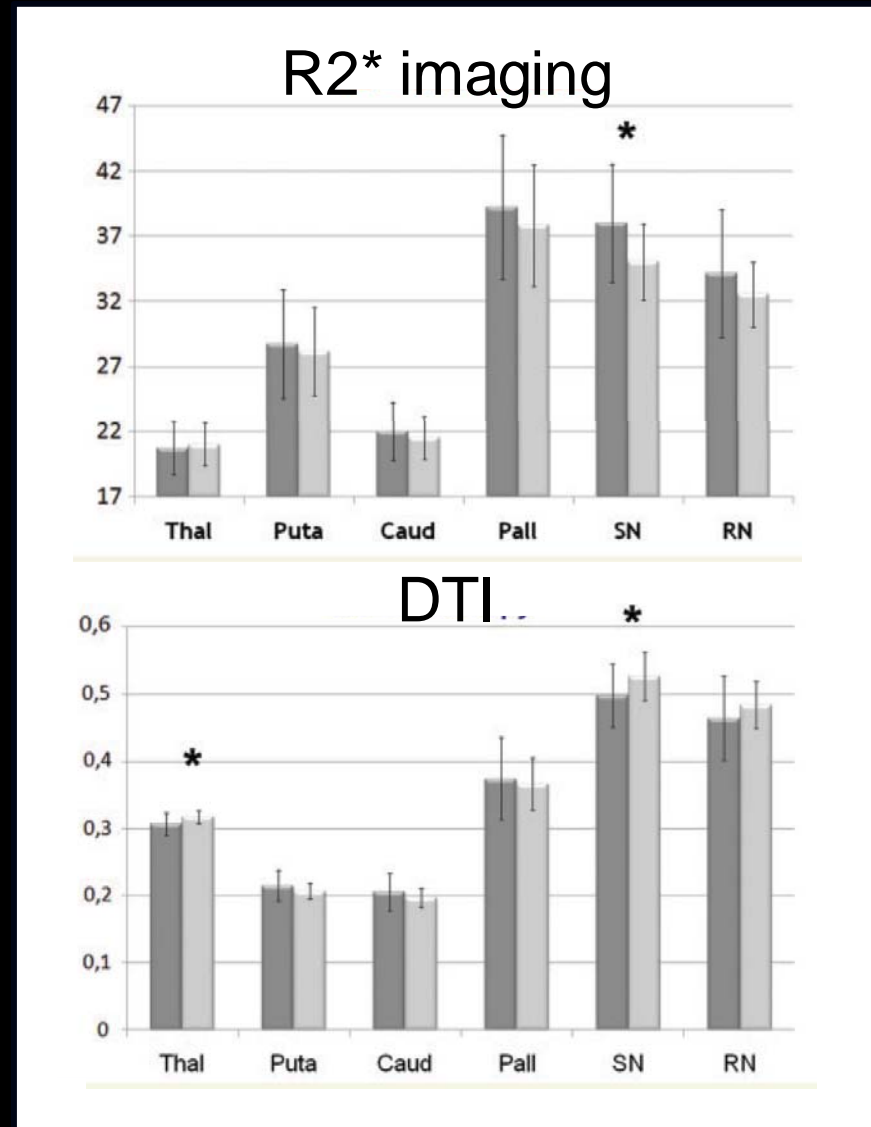# Rostral to caudal degeneration pattern

# Individual patients have reduced FA
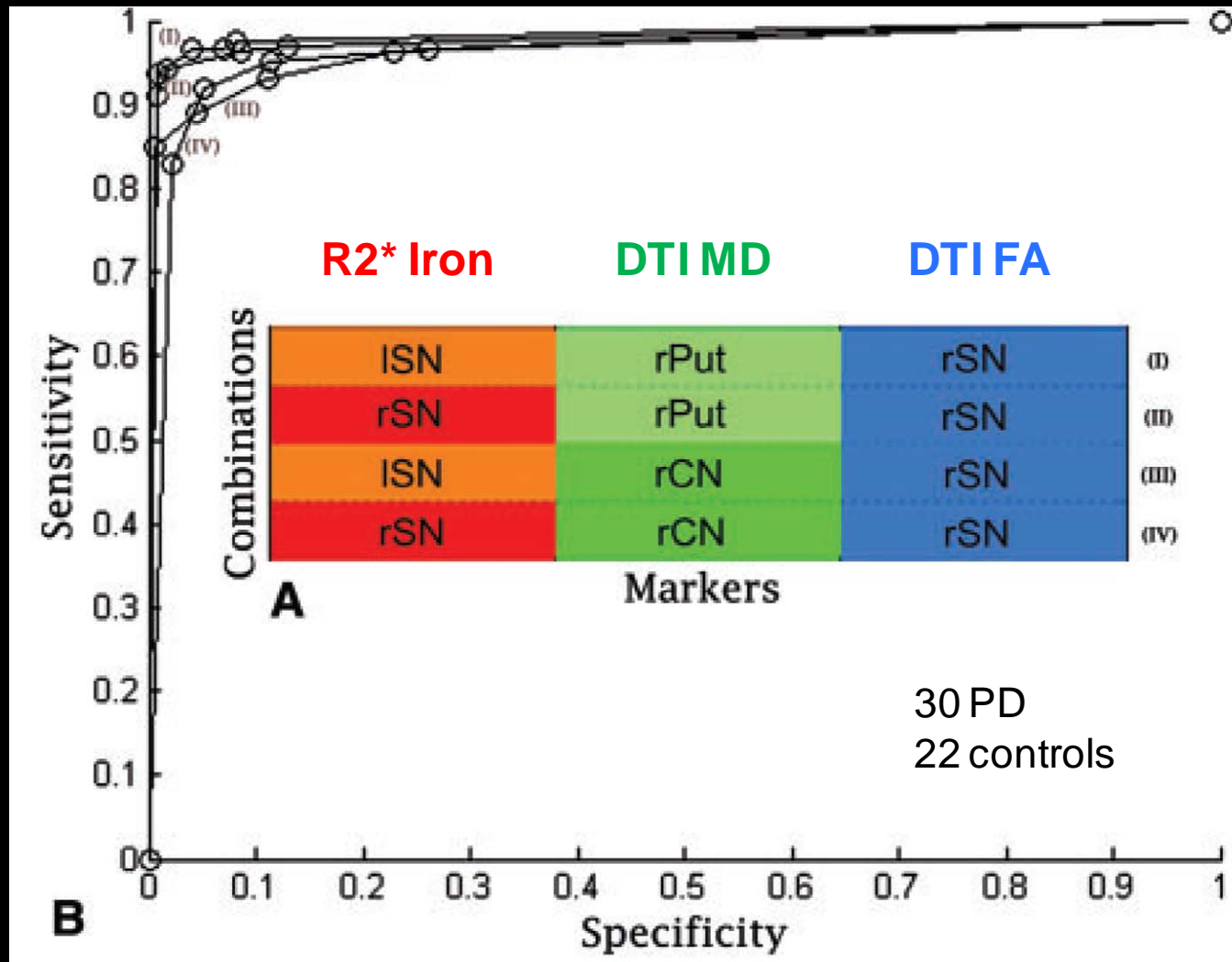


*Caudal regions provide 100% sensitivity and 100% specificity

# Combined DTI and R2* MRI based imaging

- 30 patients with PD
- 22 control subjects
- DTI and R2*
- Used voxel-based and ROI methods
- Increased R2* in SN
- Reduced FA in SN and thalamus



Peran et al., Brain, 2010

# Combined DTI and R2* MRI based imaging has <u>high</u> sensitivity

# Dorsal tier of the substantia nigra most depleted in aging
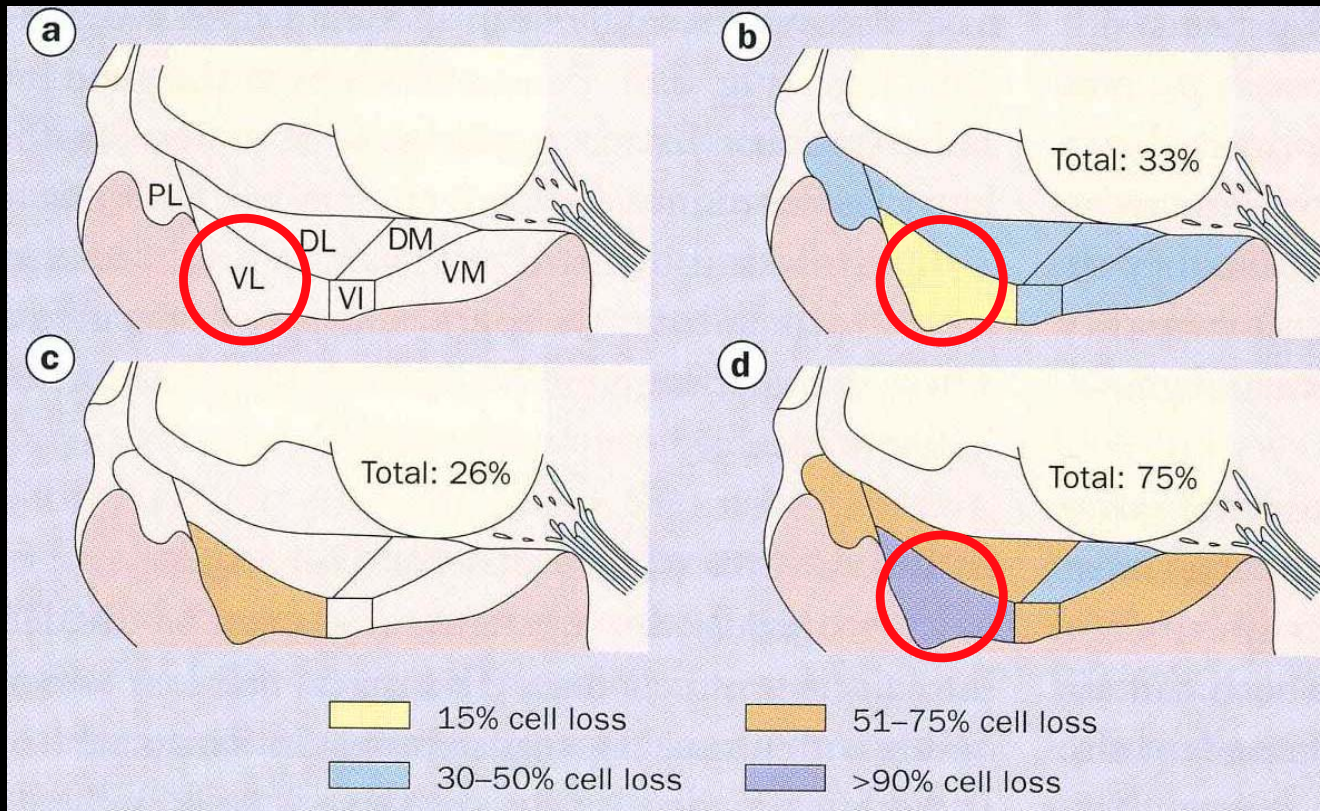


Figure 2.9. Cell loss in subregions of the substantia nigra (a) normal anatomy; PL, pars lateralis; DL, dorsolateral tier; DM, dorsomedial tier; VL, ventrolateral tier; VI, ventrointermediate tier; VM, ventromedial tier; (b) ageing (20–90 years), (c) incidental Lewy body cases, (d) Parkinson's disease [10].
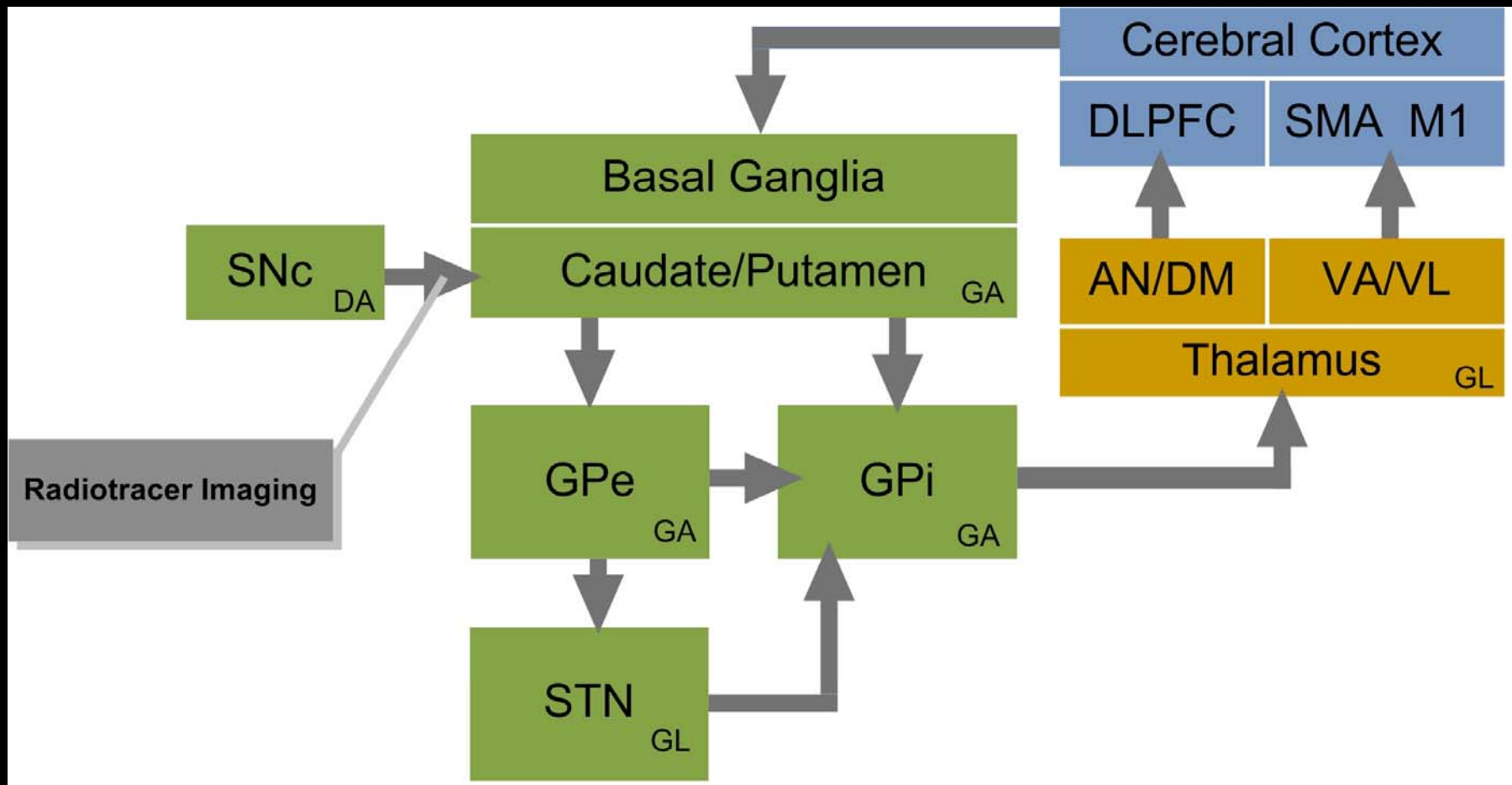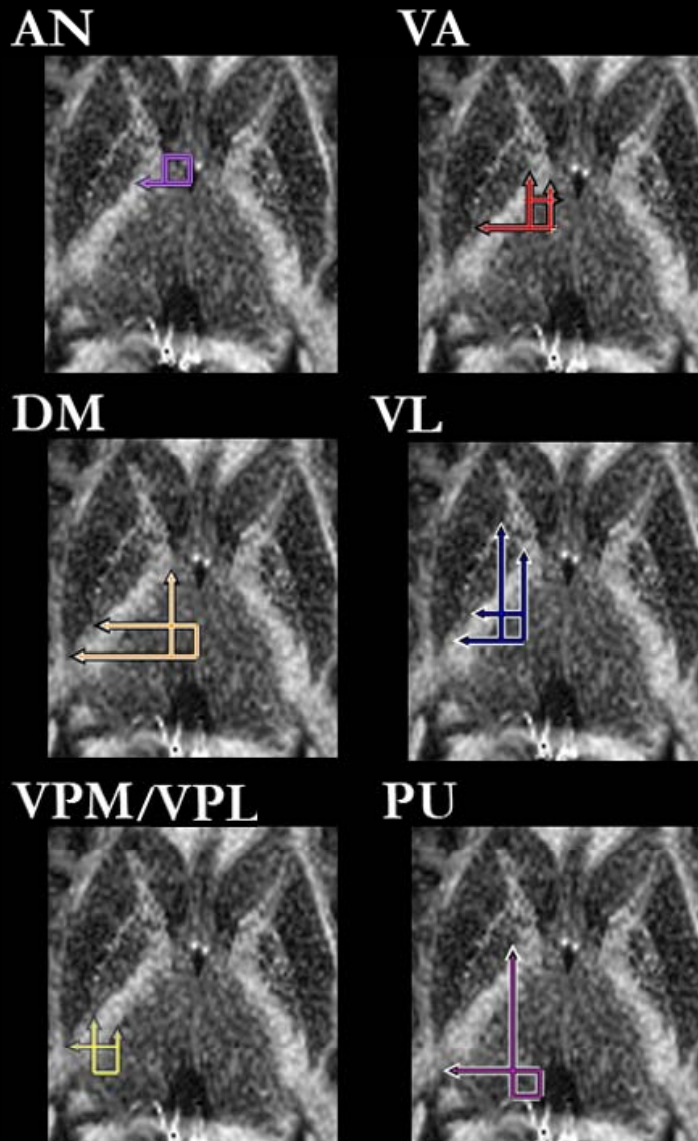
# Healthy aging affects dorsal SN
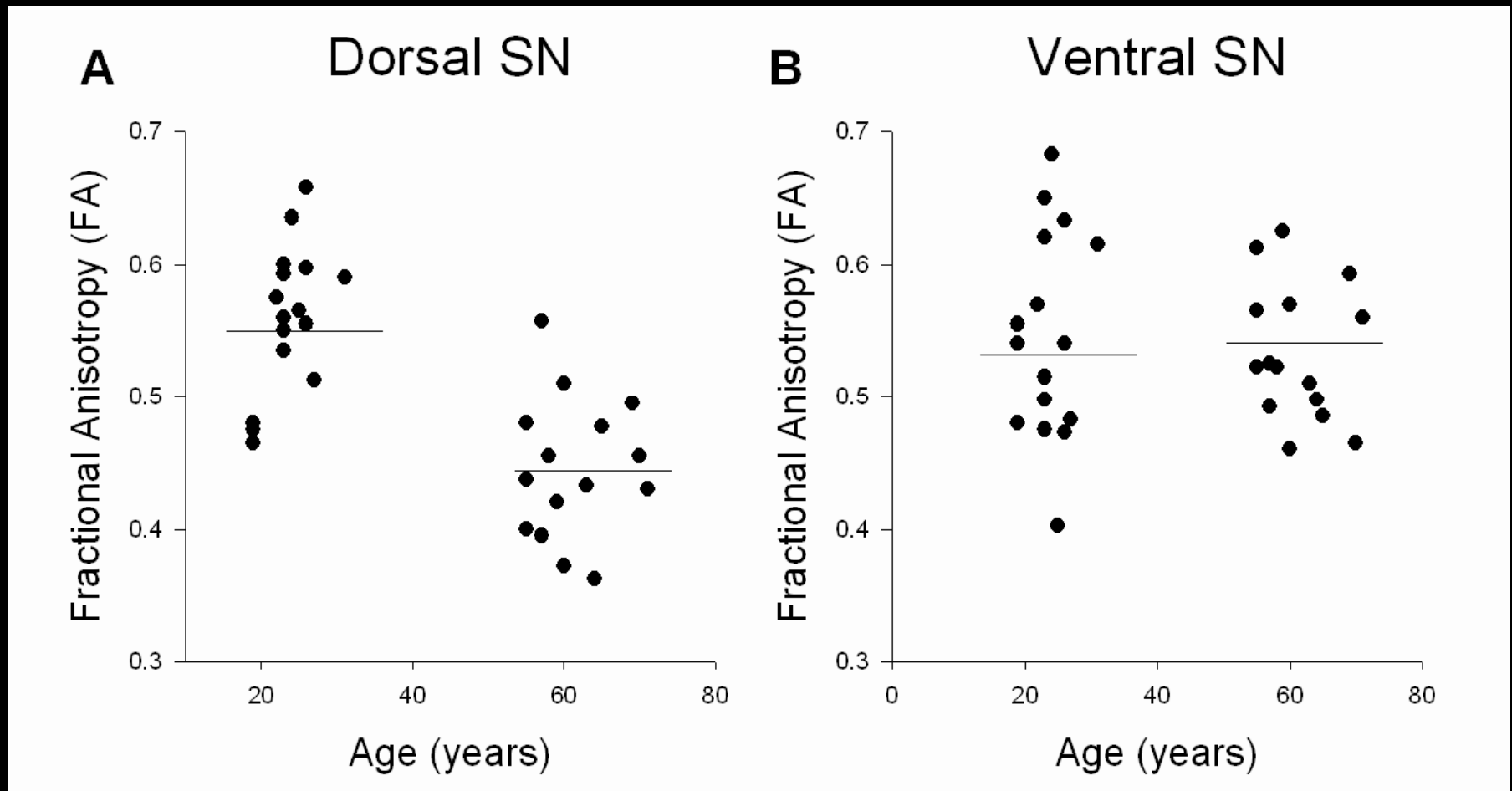


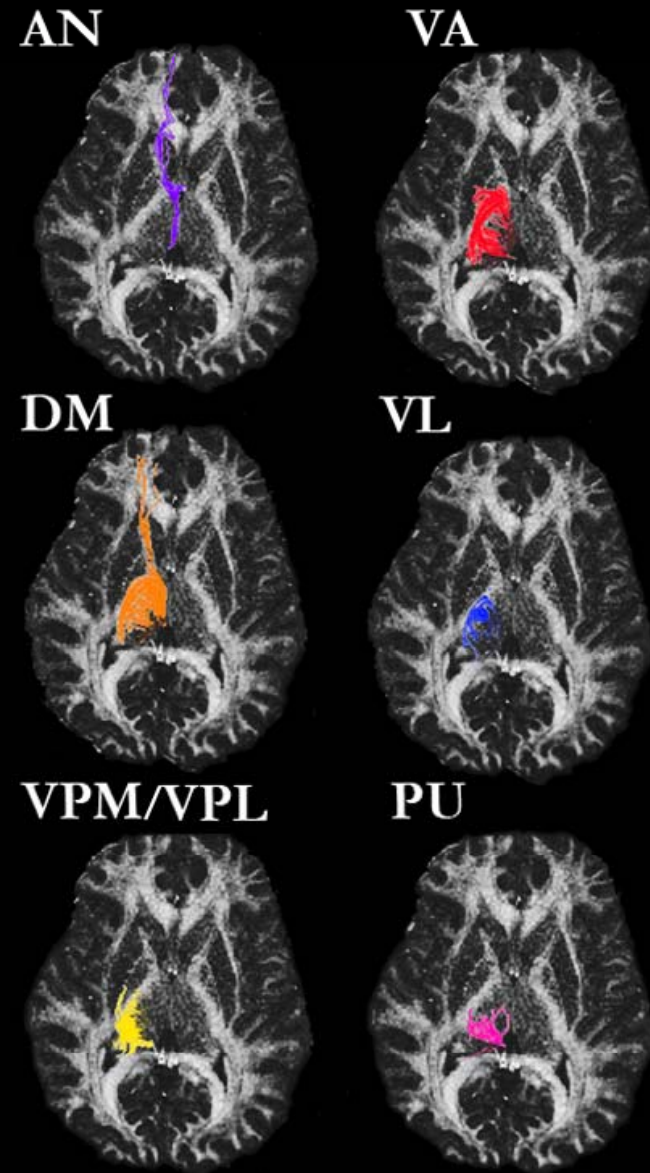**Could be different for ages greater than 71 years

Vaillancourt et al., Neurobiology of Aging, 2010

# Thalamus and PD

# Thalamus and PD



A. Seed Voxel Placement — B. Fiber Tracking

AN, VA, DM, VL, VPM/VPL, PU

*ICCs for two raters above 0.83*

# Thalamus and PD
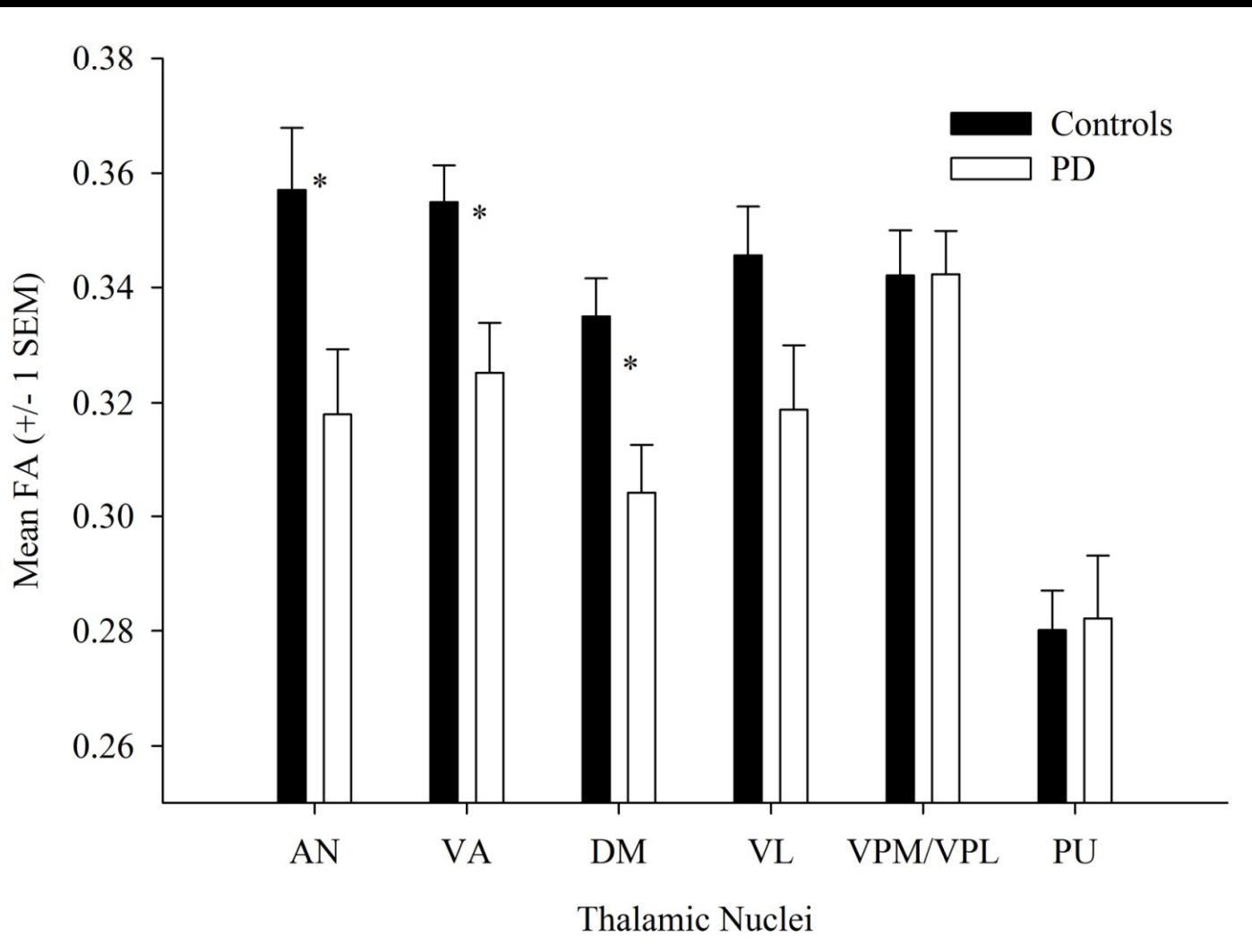
# fMRI and De Novo PD
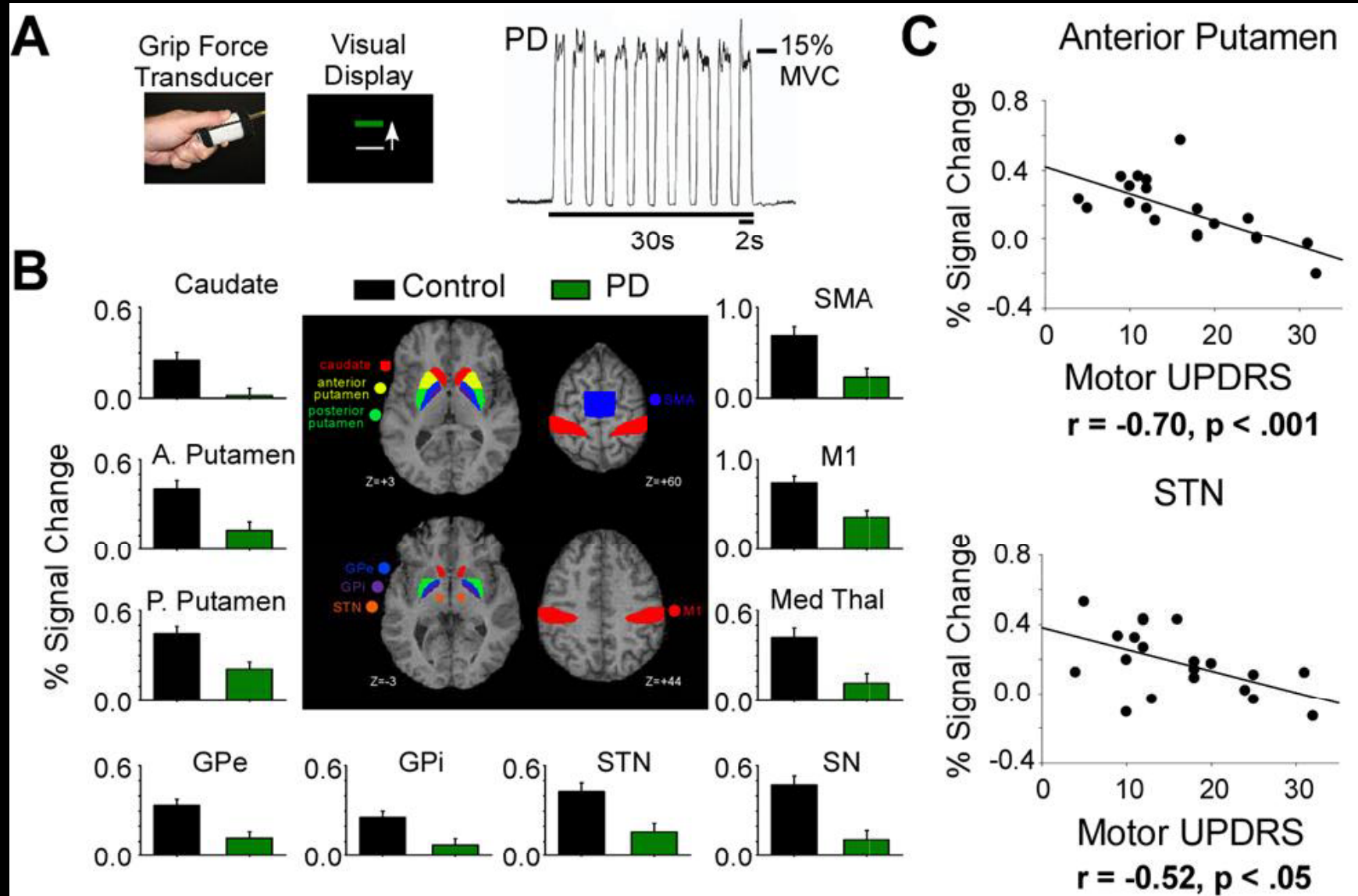
# Trait and state biomarkers

- **Trait biomarkers**
  - separating a disease from health
  - separating a disease from other diseases

- **State biomarkers**
  - tracking progression of neurodegeneration
  - tracking the efficacy of a drug acutely or chronically over time

# DTI in PD, MSA, PSP, and ET

- **Hypothesis:** diffusion tensor imaging will differentiate PD from MSA, PSP, and ET.

- **Recruitment Goal:** recruit 60 well diagnosed patients with these four movement disorders.

# DTI in PD, MSA, PSP, and ET

- <u>**What is involved:**</u>
  - One morning session (few hours)
    - Tested off DA therapy (patients do not take morning dose)
  - Structural imaging using T1 and T2
  - Diffusion tensor imaging of <u>basal ganglia</u>
  - Diffusion tensor imaging of <u>cerebellum</u>
  - Diffusion tensor imaging of <u>whole brain</u>
  - Rating scales for movement and cognition
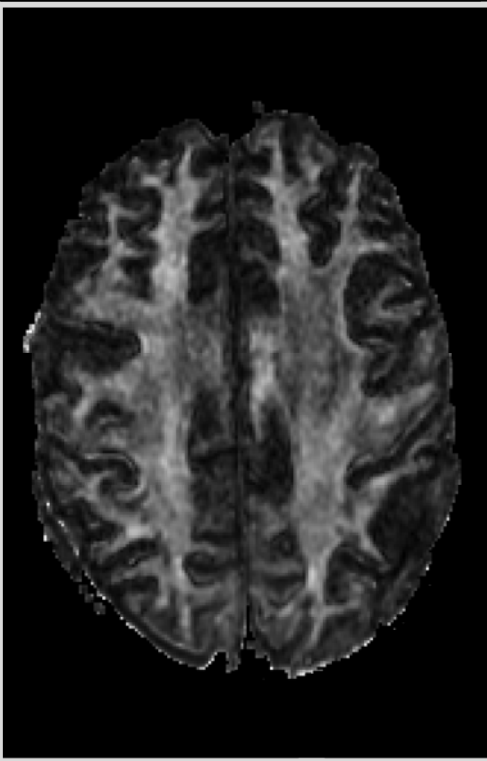
# Regions of Interest Analysis

- Basal ganglia: hand-drawn
  - Putamen, caudate, globus pallidus, substantia nigra

- Cerebellum: hand-drawn
  - Dentate, superior cerebellar peduncle (CP), middle CP, inferior CP

- Frontal and Cortical: standard ROIs

- Two raters blinded to patient status
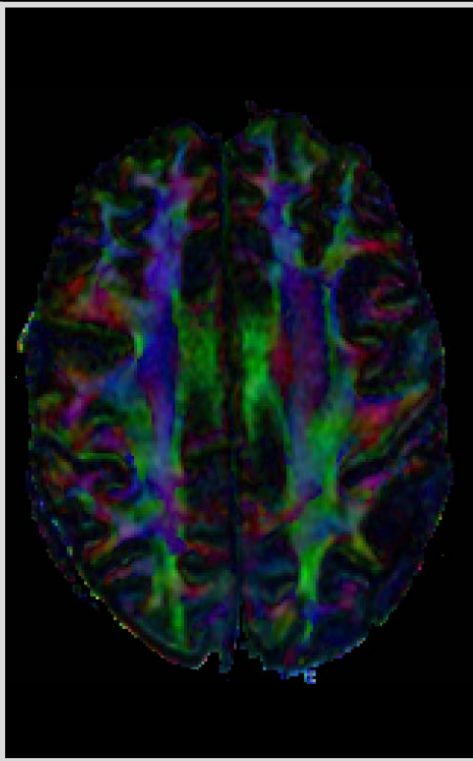
# Images we use to hand-draw ROIs
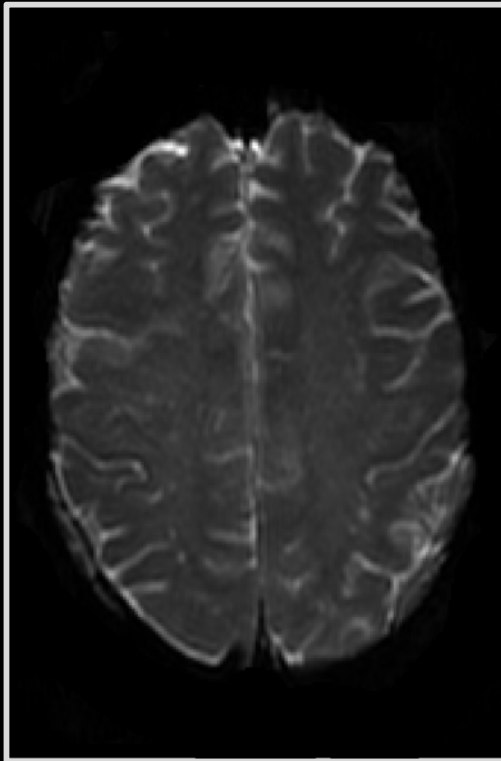
Bo image   FA image   Colormap
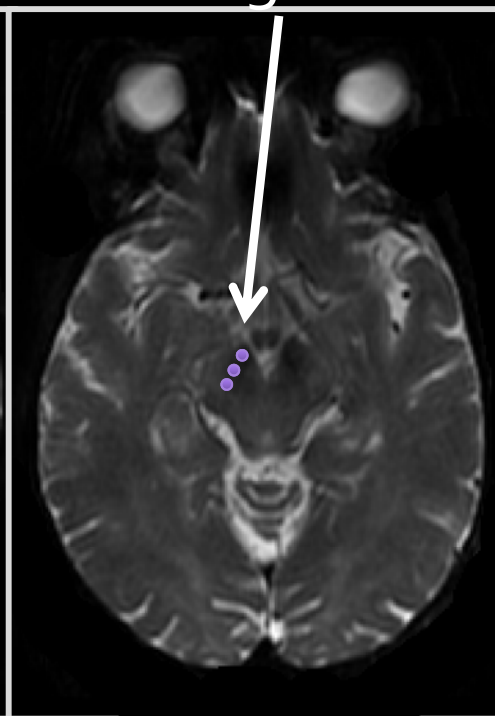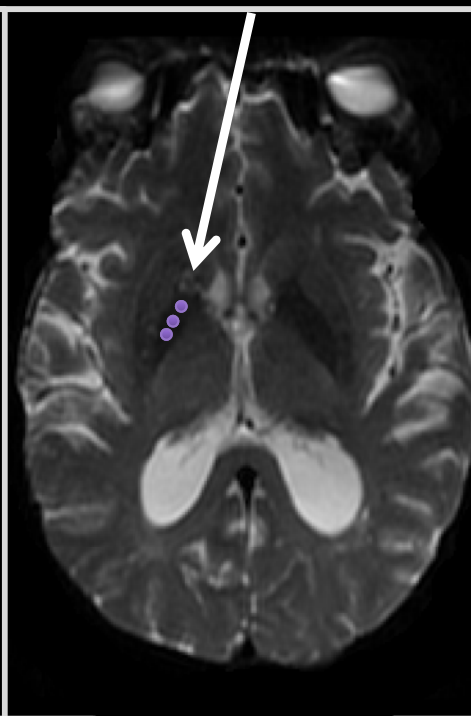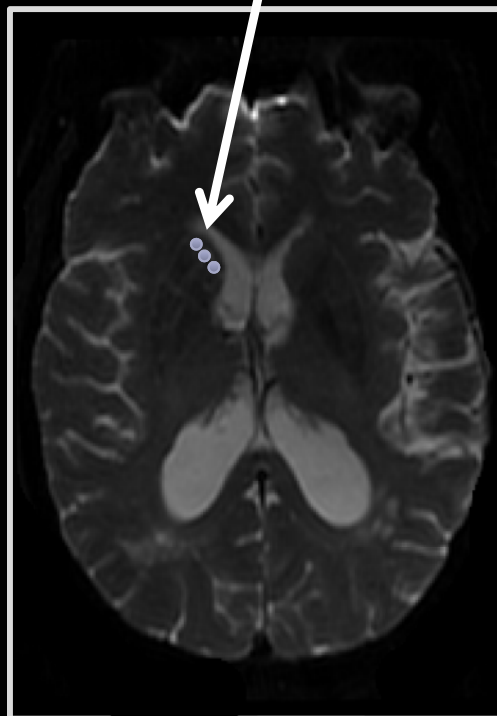


X red, Y green, Z blue

# Example ROIs for BG
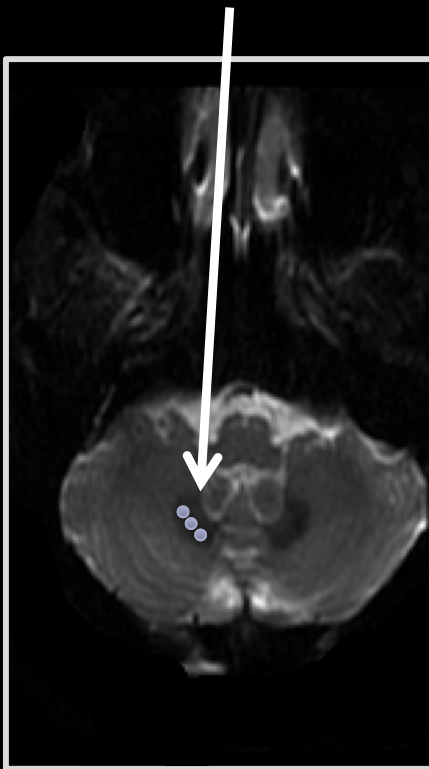


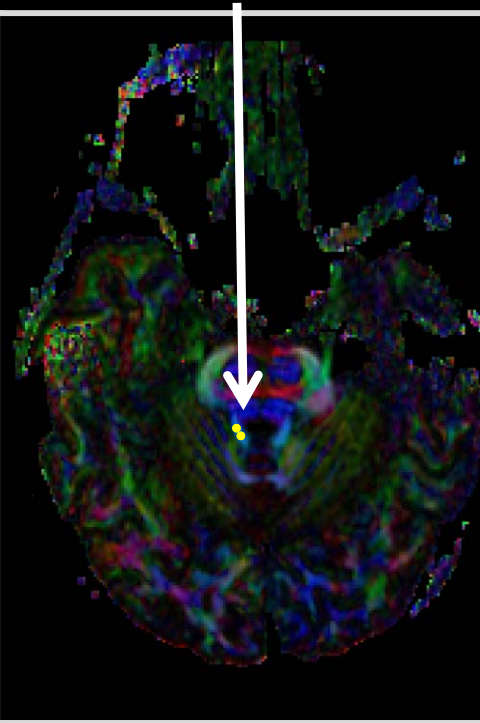Caudate      Putamen      Globus Pallidus      Substantia nigra

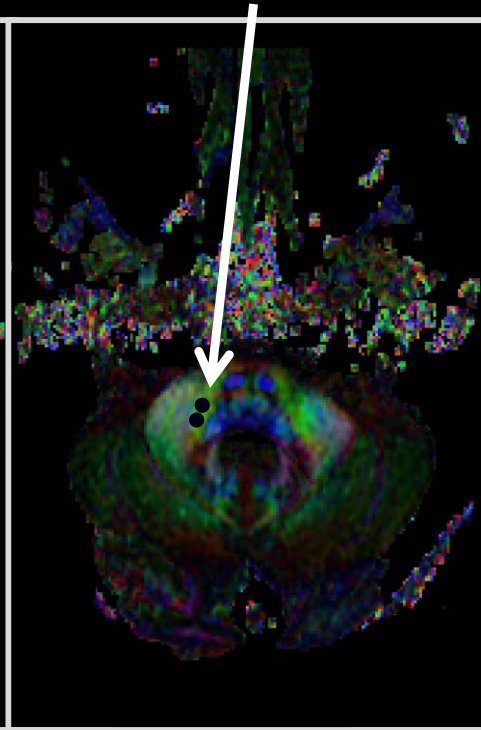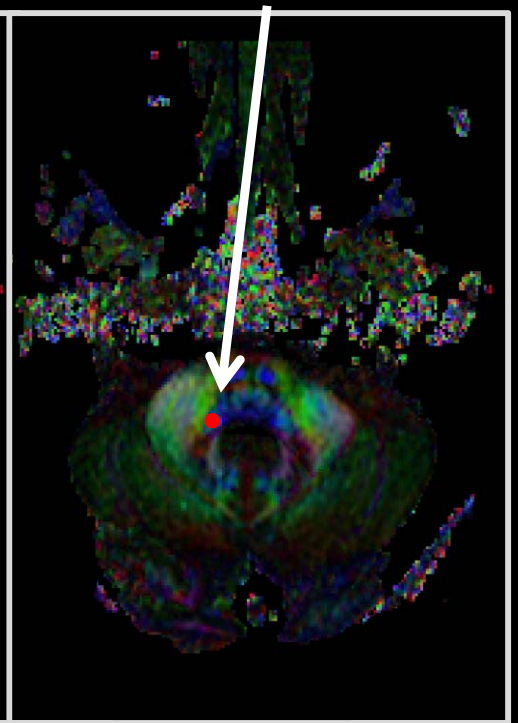# Example ROIs for Cerebellum



Dentate

Superior Cerebellar Peduncle
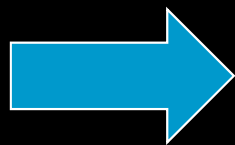
Middle Cerebellar Peduncle

Inferior Cerebellar Peduncle

# Substantia nigra of autopsied brains

- Alpha-synuclein accumulation greater in MSA and PD compared to PSP (Tong et al. 2010)

- Alpha-synuclein accumulation greater in MSA compared to PD (Tong et al. 2010)

- Reactive astrocytes greater in PSP and MSA compared to PD (Song et al. 2009)

→ Suggests that SN microstructure is fundamentally different in PD relative to atypical Parkinsonism

# Summary

- Have demonstrated that FA values from DTI in the ventral SN has high sensitivity for early stage, de novo PD

- Combined DTI and iron imaging has high sensitivity for PD (Peran et al. 2010)

- AN, DM, and VA thalamic nuclei impaired in early PD

- DTI in substantia nigra shows promise in preliminary data for differentiating PD from MSA, PSP, and ET

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Motor Control and Movement Disorders Group